REMARKS

A. Summary of Amendment to the Claims

By the present Response, no amendments have been made to the claims.

Thus, upon entry of the Response, claims 1-62 will be pending, of which claims 18-45 and 50-61 are withdrawn. Therefore claims 1-17, 46-49 and 62 remain pending and under examination.

B. Entry of New Claim 62

In the Advisory Action mailed March 24, 2009 the examiner alleged that entry of new claim 62, submitted in Applicant's Response submitted February 27, 2009 was not in compliance with the requirements of 37 C.F.R. §1.116, as no claims were cancelled and to the extent that the examiner alleged that the amendments to the claims did not advance prosecution. As the Response mailed February 27, 2009 has been noted as the submission accompanying the Request for Continued Examination, 37 C.F.R. §1.116 no longer applies. Status of the prosecution of the present application is no longer After Final.

Furthermore, in the Advisory Action mailed March 24, 2009 the examiner alleged that entry of new claim 62 would require additional search or consideration. In particular, the examiner alleged that the claim "would require further search of the prior art to identify the particular affinity required among the broad range indicated at page 18 of the specification." As the Response mailed February 27, 2009 has been noted as the submission accompanying the Request for Continued Examination, such search is respectfully requested.

The examiner also stated that "[t]he new claim 62 would also raises [sic] new issues under the first paragraph of 35 USC 112 where no particular structure that affords a particular dissociation constant, currently inappropriately expressed in the claims as 'binding affinity,' is indicated in claim 1, from which claim 62 depends. Applicant respectfully disagrees.

The examiner's attention is respectfully drawn to the language of claim 62, which depends from claim 1 and recites the particular Kd of the binding of the protease prodomain protein and the protease or variant thereof. Recitation of a Kd of less than 10nM narrows the recitation of claim 1 by further definition of the recitation of "...has binding with high affinity to a protease or variant thereof" in claim 1. Such a claim is clearly supported by the specification at page 18:

> "[t]he phrase 'binding with high affinity' as used herein refers to the ability of the protease prodomain to bind to the cognate protease with a Kd of nM to pM and ranging from about 10 nM to about 10 pM, preferably < 100 pM."

As set forth in MPEP §2163, "[t]o satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." With regard to the biochemical arts, the Federal Circuit has held that "…there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure." (emphasis added) *Falkner v. Inglis*, 448 F.3d 1357, 1366, 79 USPQ2d 1001, 1007 (Fed. Cir. 2006).

As pending in the claimed invention, independent claim 1 contains both structural and functional requirements. New claim 62 depends from claim 1 and, by virtue of its dependency, must contain all limitations recited in claim 1. In claim 1 the nucleic acid construct encodes a fusion protein that structurally comprises the elements 1) coding sequence for a protein of interest and 2) coding sequence for a protease prodomain protein, where the fusion protein functionally has the two elements operatively linked and where, functionally, the protease prodomain protein binds a protease or a variant thereof with high affinity. New claim 62 recites that the disassociation constant of the binding is less than 10nM, as a measure of the functional binding affinity of claim 1.

The examiner's attention is respectfully drawn to the detailed discussion of binding affinity and disassociation constants as provided in the Response mailed February 27, 2009. In summary, the measure of disassociation constant is provided as evidence of a high binding affinity, as recited in claim 1. Binding affinity and disassociation constants are separate measurements. As previously explained in detail, the affinity of a protein for a protease is the ability to bind to the protease and stay bound. Low disassociation constant is indicative of high binding affinity because the bound elements remain bound to one another and do not disassociate.

Use of the term "binding affinity" in claim 1 is appropriate, contrary to the examiner's assertion. Inclusion of the phrase "high affinity" describes the way that the protease prodomain protein and the protease or variant thereof bind to one another and stay bound. High affinity is the reason that the protease prodomain protein and the protease or variant thereof bind and remain bound, the low dissociation constant is a measure of the resultant bound complex.

At the time of filing of the present invention, one skilled in the art could have reasonably concluded that the inventor had possession of the claimed construct, comprising a coding sequence for a protein of interest and a coding sequence for a protease prodomain protein, wherein the fusion protein comprises the protein of interest operatively linked to the protease prodomain protein and wherein the protease prodomain protein has binding with high affinity to a protease or a variant thereof, as evidenced by a disassociation constant of 10nM or less.

Accordingly, new claim 62 meets the written description requirement of 35 U.S.C. §112.

C. Rejection of Claims Under 35 U.S.C. § 112

In the Advisory Action mailed March 24, 2009 the examiner alleges that "introductions of 'protease' and 'protein' in claims 3, 7, and 13 does not remove these claims from the rejection of record under the second paragraph of 35 USC 112." Previously the examiner rejected claims 3, 7, and 13 under 35 U.S.C. §112, second paragraph as indefinite for recitation of the phrase "…prodomain is modified to bind subtilisin or a variant thereof with increased affinity as compared to an unmodified prodomain protein…" in each of such claims.

In response, applicant provided extensive evidence that many different types of subtilisins are known in the art (Specification, p. 3) and that variants of subtilisins are known (Appendix B to Response mailed February 27, 2009.) In the Advisory Action the examiner responded that "[t]he phrase variant remains indefinite without the identification [sic] a particular structure with which comparison can be made." Applicant respectfully disagrees.

The claims recite "subtilisin or variants thereof." Clearly the claims encompass any subtilisin produced by any species of bacteria or fungi. Variants thereof are variants of subtilisin, including subtilisin-like proteases which, by definition, are not subtilisins themselves. As previously noted in the Response mailed February 27, 2009, various mutations of subtilisin were known in the art at the time of filing of the present application, as described in the specification at page 3, lines 9-14. The terms "mutation," "variant" and "subtilisin-like proteases" are all defined in the application at pages 13-14. Appendix B to the Response mailed February 27, 2009 provided evidence that subtilisin-like proteases have a widely recognized and consistent mechanistic and structural definition that is known and recognized by those of skill in the art.

From the description in the specification and with the knowledge in the art at the time of filing of

the application, one of skill in the art would be able to generate a construct, as claimed, comprising a protease prodomain protein with increased binding affinity for subtilisin or a variant of subtilisin.

Withdrawal of the rejection of claims 3, 7, and 13 under 35 U.S.C. §112, second paragraph as indefinite is respectfully requested.

D. Rejection of Claims Under 35 U.S.C. § 102

In the Advisory Action mailed March 24, 2009 the examiner alleged that "the claim amendments cannot displace the anticipatory disclosure of Van Rooijen et al. as applied to the claims 1, 46 and 47 under 35 USC 102(e)." Applicant respectfully disagrees.

As set forth above in detail and further in the Response mailed February 27, 2009 the claims of the application require a construct with both structural and functional aspects. Van Rooijen et al. do not provide a nucleic acid construct encoding protein portions with the characteristics recited in the claims of the present application, namely, proteins with high binding affinity for a protease or variant thereof.

In the Response mailed February 27, 2009 Applicant provided a detailed explanation of how the claimed invention varies from Van Rooijen et al. in that Van Rooijen et al. provide a construct encoding a fusion polypeptide that is both structurally and functionally different from the fusion proteins produced from the presently claimed constructs of claims 1, 46 and 47.

Van Rooijen et al. do not provide a showing of a construct encoding a fusion protein comprising a prodomain protein with a high affinity for a protease. In fact, high affinity for subtilisin and other proteases leads to substrate inhibition and poor turnover in the processing of fusion proteins. Very high affinity, as claimed, leads to only a single turnover, due to the continued binding of the protease and the prodomain portion (or the second protein, in claims 46 and 47).

As Van Rooijen et al. do not describe a nucleic acid construct as set forth in claims 1, 46 or 47, Van Rooijen et al. do not anticipate the claimed invention. Accordingly, withdrawal of the rejection of claims 1, 46, and 47 under 35 U.S.C. § 102(e) as being anticipated by Van Rooijen et al. is respectfully requested.

E. Limitations based on Dissociation Constants

In the Advisory Action mailed March 24, 2009 the examiner suggests that, rather than add new claim 62, applicant add the Kd limitation to other pending claims. Applicant thanks the examiner for the suggestion, but does not wish to add such limitations to other claims at this time. Applicant respectfully reserves the right to make such claim amendments at a later date, if desired.

By entry of the Response mailed February 27, 2009, new claim 62 is presently pending and under examination.

CONCLUSION

Based on the foregoing, all of Applicant's pending claims 1-17, 46-49 and 62 are patentably distinguished over the art, and in form and condition for allowance. The examiner is requested to favorably consider the foregoing, and to responsively issue a -Notice of Allowance.

If any issues require further resolution, the examiner is requested to contact the undersigned attorney at (919) 419-9350 to discuss same.

Respectfully submitted,

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